

PATENT  
DOCKET NUMBER P41 9755

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of: ) Group Art Unit 1804  
EVANS ET AL. )  
 ) Examiner: Jon P. Weber  
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Serial No.: 08/244,857 )  
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Filed: June 14, 1994 )  
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For: Means for the Modulation of )  
Processes Mediated by Retinoid )  
Receptors and Compounds )  
Useful Therefor )

DECLARATION OF DR. ROBERT B. STEIN

I, ROBERT B. STEIN, M.D., Ph.D., declare as follows:

1. I have personal knowledge of the facts stated herein and if called as a witness I could and would competently testify to the following:

2. I am a Senior Vice President and Chief Scientific Officer at Ligand Pharmaceuticals Incorporated. In 1972, I received two bachelor of science degrees with honors in biology and chemistry from Indiana University. In 1979, I received my M.D. and also a Ph.D. in physiology and pharmacology from Duke University. Continuing at Duke, I completed a four year residency in clinical and anatomical pathology and in both of these areas I am presently Board Certified. Attached hereto as Exhibit A is a true and correct copy of my most recent Curriculum Vitae. Since completing my residence, I have been actively involved in pharmacology and physiology with an emphasis on the application of drugs to disease. In particular, I have extensively studied and researched the pathology of cancer,

including the nature of cancer, its diagnosis, and the monitoring and assessment of treatments for cancer.

3. I have read and analyzed the parent of the above-identified application, *i.e.*, Evans et al.'s U.S. Patent Application Serial No. 07/809,980 ("the '980 application"), filed on December 18, 1991. In addition, I have read and analyzed claims 51, 52 and 53, which I understand were recently filed as part of a preliminary amendment in the above-identified application, which is a continuation-in-part of the '980 application.

4. At the time the '980 application was filed, it was well known in the art that cancers can be classified by their tissue of origin. Cancers develop from three principal tissues of origin: lymphoid and blood forming tissue, connective tissue, and epithelial tissue. Cancers derived from lymphoid and blood forming tissue are known as lymphomas and leukemias. Cancers derived from connective tissue are known as sarcomas. Cancers derived from epithelial tissue are known as carcinomas. Attached as Exhibit B is a true and correct copy of an excerpt from "Cancer Medicine", Microsoft Encarta (1994) (See marked portions), and attached as Exhibit C is a true and correct copy of pages 242 and 243 of "Robbins Pathologic Basis of Disease", R.S. Cotran, M.D., V. Kumar, M.D. and S.L. Robbins, M.D., eds., W.B. Saunders Company, Philadelphia, Pennsylvania (1994) (See marked portions). Exhibits B and C further set forth the three principal tissues of origin used in classifying cancers.

5. In my opinion, the specification of the '980 application teaches and discloses how to treat and prevent cancers of epithelial origin with 9-*cis* retinoic acid, as required by claims 51, 52 and 53. Specifically, the '980 application refers to "in vivo modulation of malignant cell development, such as occurs, for example, in acute promyelocytic leukemia, testicular cancer, lung cancer, and the like." '980 application, p. 11, lines 19-22. The quoted language reasonably conveys to me and those of ordinary skill in the art that the inventors of the '980 application contemplated and disclosed the treatment

and prevention of cancers derived from epithelial tissues of origin with 9-*cis* retinoic acid. I base my opinion on the fact that the vast majority of lung cancers and many testicular cancers are of epithelial origin. Attached as Exhibit D is a true and correct copy of page 73 of "Lung Cancer", B.E. Johnson, M.D. and D.H. Johnson, M.D., eds., Wiley-Liss, Inc., New York, New York (1995) (See marked portions), which shows the relative incidence of lung cancer of epithelial origin. Consequently, those of skill in the art, upon reading the disclosure of the '980 application, would readily recognize that the inventors of the '980 application had described a method of preventing and treating cancers of epithelial origin (*i.e.*, carcinomas) with 9-*cis* retinoic acid.

6. I hereby further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further, that these statements are made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

Dated: August 10, 1995

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ROBERT B. STEIN, M.D., Ph.D.